NEUROGEN CORP *WO 200059888-A1

1999.04.02 1999-285420(+1999US-127624) (2000.10.12) C07D 235/14, A61K 31/4045, 31/4184, G01N 33/50, A61P 25/00, C07D 209/14

New N-benzimidazolylmethyl and N-indolylmethyl benzamide derivatives, useful as corticotropin releasing factor (CRF) modulators for treating e.g. depression, anxiety, cardiovascular and eating disorders (Eng)

C2000-195862 N(AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW)

Addnl. Data: HORVATH R F, GE P, YOON T, HUTCHISON A

2000.03.31 2000WO-US08570, 1999.04.02 1999US-285420

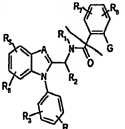
NOVELTY

N-benzimidazolylmethyl and N-indolylmethyl benzamide derivatives (I) are new.

B(4-E5, 6-D1, 6-D5, 12-K4F, 14-E11, 14-E12, 14-F1, 14-J1A1, 14-J1B4) .7

DETAILED DESCRIPTION

N-benzimidazolylmethyl and N-indolylmethyl benzamide derivatives of formula (I) and their salts are new.



reactant

(I)

A = N or CY;

Y = H or 1-6C alkyl;

R_1 = H, 1-6C alkyl or hydroxy 1-6C alkyl;

R_2 = H or 1-6C alkyl, provided R_2 is H when A is CY;

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G, R_3, R_4 = H, halo, CF_3, OCF_3, CN, 1-6C alkyl, 1-6C alkoxy, OH, hydroxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, SH, 1-6C alkylthio, thio 1-6C alkyl or 1-6C alkylthio 1-6C alkyl; and

R_5- R_8 = H, halo, CF_3, OCF_3, CN, 1-6C alkyl, 1-6C alkoxy, OH, SH, 1-6C alkoxy 1-6C alkoxy, hydroxy 1-6C alkoxy, hydroxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, amino, mono- or dialkylamino, 1-6C alkylthio, thio 1-6C alkyl or 1-6C alkylthio 1-6C alkyl.

INDEPENDENT CLAIMS are included for:

(1) a packaged pharmaceutical composition comprising (I), a container and instructions;

(2) a method of localizing CRF receptors in tissue section samples by contacting the sample with labelled (I) and binding, washing the sample to remove unbound compound, and detecting the bound compound; and

(3) preparation of (I).

ACTIVITY

Tranquilizer; antidepressant; cardiant, anorectic; anabolic: nootropic; neuroprotective; antiparkinsonian; anticonvulsant; anti-HIV; vasotropic; vulnerary; antiaddictive; analgesic.

MECHANISM OF ACTION

CRF receptor modulator.

In a standard assay of CRF binding, the compounds (I) exhibit an IC_{50} value of less than 1 micro M, preferably less than 100, especially less than 10 nM (claimed).

USE

(I) is used to treat stress, anxiety, depression, cardiovascular disorders, obesity and eating disorders, drug addiction, obsessive-compulsive disorders, stress, neurological disorders such as supranuclear palsy, AIDS related dementia, multi infarct dementia, Alzheimer's disease, Huntingdon's disease and Parkinson's disease, ischemia, trauma, fibromyalgia and epilepsy. (I) can also be used as a probe, for localizing CRF receptors, inhibiting binding of CRF to the CRF1 receptor in IMR32 cells, and for altering the signal-transducing activity of a cell surface CRF1 receptor (all claimed).

SPECIFIC COMPOUNDS

68 compounds (I) are specifically claimed, e.g. N-{[1-(4-methoxyphenyl)indol-2-yl]methyl}-N-(methylethyl)(2,4,6-trimethylphenyl)carboxamide (Ia).

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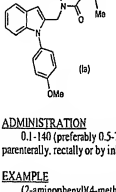

(Ia)

ADMINISTRATION

0.1-140 (preferably 0.5-7) mg/kg/day e.g. orally, topically, parenterally, rectally or by inhalation.

EXAMPLE

(2-aminophenyl)(4-methoxy-2-methylphenyl)amine (60 g) in chloroform (350 ml) was stirred with imidate (59 g) at room temperature for one hour. $NaHCO_3$ (100 ml) was added, and extracted with dichloromethane (4x150 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography to give 1-[2-(chloromethyl)benzimidazolyl]-4-methoxy-2-methylbenzene (IIa) (50 g, 65%). (IIa) (3 g) in acetonitrile (20 ml) was reacted with isopropylamine (5 ml) at 50°C in a sealed tube for one hour. Solvent was removed *in vacuo*, and the residue partitioned between ethyl acetate (30 ml) and 1N NaOH solution (10 ml). The organic layer was dried (Na_2SO_4) to give {[1-(4-methoxy-2-methylphenyl)benzimidazol-2-yl]methyl}(methylethyl)amine (3.1 g, 98%). This amine was stirred with 2,4,6-trimethylbenzoylchloride (2.6 ml) in 1:1 dichloromethane:$NaHCO_3$ solution (30 ml) for one hour at room temperature. The mixture was partitioned, the organic layer dried, and the solvent removed *in vacuo*. The crystallized product was triturated with ether, filtered and dried to give N-[[1-(4-methoxy-2-methylphenyl)benzimidazol-2-yl]methyl]-N-(methylethyl)(2,4,6-trimethylphenyl)carboxamide (Ia) (4.4 g, 92%).

DEFINITIONS

Preferred Definitions :

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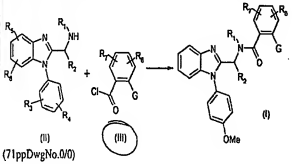
(con't)

R_1 = H;
Q = trimethylphenyl;
R_3, R_4 = H, F, Cl, OH, CF_3 or Me;
provided that R_3 and R_4 can not both be H.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) is prepared by e.g. reacting a benzimidazole compound of formula (II) with a benzyl chloride of formula (III) to give (I; A = N).



(II) (III) (I)

(71ppDwgNo.0/0)